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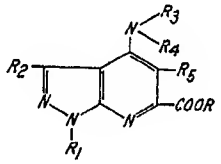
(72) Inventors THEODOR DENZEL and HANS HOEHN

(54) DERIVATIVES OF PYRAZOLOPYRIDINE-5-CARBOXYLIC ACIDS AND ESTERS

(71) We, E. R. SQUIBB & SONS, INC., a corporation organised and existing under the laws of the State of Delaware, United States of America, residing at Lawrenceville-Princeton Road, Princeton, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention provides amino derivatives of pyrazolo - [3,4 - b]pyridine - 6 - carboxylic acids, esters and salts of these compounds as well as processes for producing them. More specifically, the invention provides compounds of the formula



(I)

wherein R is hydrogen or lower alkyl; R_1 is hydrogen, lower alkyl, phenyl or phenyl-lower alkyl; R_2 is hydrogen or lower alkyl; R_3 and R_4 each is hydrogen, lower alkyl, phenyl, R_8, R_7-phenyl, R_6, R_7-phenyl-lower alkyl or di-lower alkylamino-lower alkyl, or R_3 and R_4 together with the nitrogen to which they are attached form one of the heterocyclic R_8, R_9-pyrrolidino, R_8, R_9-piperidino, R_8, R_9-pyrazolyl, A_8, R_9-dihydropyridazinyl or R_8 R_9-piperazinyl; R_5 is hydrogen, lower alkyl, phenyl, phenyl-lower alkyl or halogen; R_6 and R_7 each is hydrogen, lower alkyl, trifluoromethyl or carboxy, R_8 and R_9 each is hydrogen, lower alkyl or hydroxy-lower alkyl, including their physiologically acceptable acid addition salts.

Preferably only one of R_6 and R_7 is trifluoromethyl or carboxy, and preferably only one of R_3 and R_4 is di-lower alkylamino-lower alkyl (preferably only one of the last named group). It is also preferred that not more than one of R_8 and R_9 is a hydroxy-lower alkyl group.

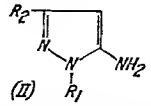
The lower alkyl groups in any of the foregoing radicals are straight or branched chain hydrocarbon groups of up to seven carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl or t-butyl. The one to four carbon groups are preferred.

All four halogens are contemplated but chlorine and bromine are preferred.

The products of the examples, which are representative of the various compounds of this invention, constitute preferred embodiments. Preferably R_3 is hydrogen, particularly when R_4 includes a cyclic substituent. Preferred heterocyclic radicals are those shown in the examples, especially piperidino and piperazino and their methyl and hydroxyethyl derivatives. Especially preferred compounds of formula I are those wherein R is hydrogen or lower alkyl, especially ethyl, R_1 is hydrogen, ethyl or butyl, R_2 is hydrogen or methyl, R_3 is ethyl, propyl or butyl, R_4 is hydrogen or ethyl and R_5 is hydrogen, methyl or chlorine.

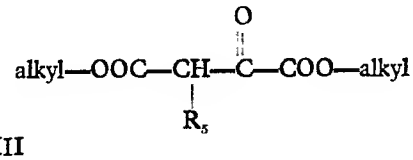
The compounds of formula I may be produced by the following series of reactions. The symbols in the formulae have the meaning previously described.

A 5-aminopyrazole of the formula



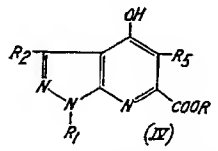
(II)

[produced analogous to the procedure described in Z.f. Chemie *10*, 386 (1970)], is made to react with an oxalacetic acid ester of the formula



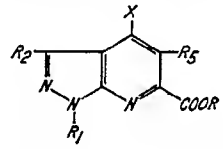
III

by heating at a temperature of about 110—120° C. in an acidic solvent such as acetic acid, analogous to the procedure in Pharmazie, 26, 732 (1971). The resulting compound of the formula



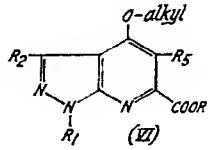
(IV)

with the hydroxy group in the 4-position is refluxed for several hours with a phosphorus halide such as phosphorus oxychloride to obtain the intermediate of the formula



V

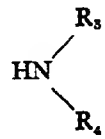
wherein X is halogen, preferably chlorine or bromine. Instead of halogenating, reaction of the compounds of formula IV with an alkyl halide in the presence of an inorganic base, such as potassium carbonate, produces a compound of the formula



(VI)

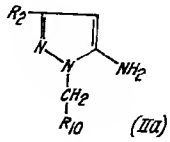
The products of formula I are then prepared from compounds of formula V or VI by reaction with the appropriate primary or secondary amine of the formula

(VII)



This reaction is effected by treating the reactants either at room or elevated temperatures. In some cases it may be advantageous to make use of an autoclave.

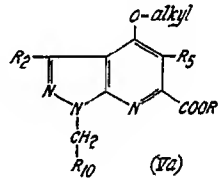
A product of formula I wherein R_1 is hydrogen is produced by a modification of the foregoing procedure. According to this modification, a 5-aminopyrazole of formula II, wherein R_1 is an arylmethyl group, or a heteromethyl group is used. This starting material has the formula



(IIa)

wherein R_{10} is an aromatic or heterocyclic nucleus such as phenyl, furyl, pyridyl, or pyrimidyl.

This material is processed as described above through the reaction with the oxalacetic acid ester of formula III to obtain a compound of formula IV with a hydroxy group in the 4-position. Then alkylating leads to a compound of the formula



(Va)

At this point, the compound of formula Va is oxidized with an oxidizing agent such as selenium dioxide in a high boiling solvent such as diethyleneglycol dimethylether at about 160°. This yields a compound of formula VI wherein R_1 is hydrogen. This product may be treated with a primary or secondary amine as described above.

The bases of formula I form salts by reaction with a variety of inorganic and organic acids providing acid addition salts including, for example, hydrohalides (especially the hydrochloride), sulfate, nitrate, phosphate, oxalate, tartrate, malate, citrate, acetate, ascorbate, succinate, benzenesulfonate, cyclohexanesulfonate, cyclohexanesulfamate and toluenesulfonate. The acid addition salts frequently provide a convenient means for isolating the product, e.g., by forming and precipitating the salt in an appropriate menstruum in which the salt is insoluble, then after separation of the salt, neutralizing with a base such as barium hydroxide or sodium hydroxide, to obtain the free base of formula I. Other salts may then be formed from the free base by reaction with an equivalent of acid.

Compounds of this invention have been found to be central nervous system depressants and may be used as tranquilizers or ataractic agents for the relief of anxiety and tension states, for example, in mice, cats, rats, dogs and other mammalian species, in the same manner as chlordiazepoxide. For this purpose a compound or mixture of compounds of formula I, or non-toxic, physiologically acceptable acid addition salt thereof, may be administered orally or parenterally in a pharmaceutical preparation including a solid or liquid carrier, e.g. in a conventional dosage form such as tablet, capsule, or sterile injectable preparation. A single dose, or preferably 2 to 4 divided daily doses, provided on a basis of about 1 to 50 mg. per kilogram per day, preferably about 2 to 15 mg. per kilogram per day, is appropriate. These may be conventionally formulated in an oral or parenteral dosage form by compounding about 10 to 250 mg. per unit of dosage with conventional vehicle, excipient, binder, preservative, stabilizer, or flavor as called for by accepted pharmaceutical practice.

These compounds also increase the intracellular concentration of adenosine - 3',5'-cyclic monophosphate, and thus by the administration of about 1 to 100 mg/kg/day, preferably about 10 to 50 mg/kg., in single or two to four divided doses in conventional oral or parenteral dosage forms such as those described above may be used to alleviate the symptoms of asthma.

Compounds of this invention have also been found to have antiinflammatory properties and to be capable of use as antiinflammatory agents, for example, to reduce local inflammatory conditions such as those of an oedematous nature or resulting from proliferation of connective tissue in various mammalian species such as rats and dogs when given orally in dosages of about 5 to 50 mg/kg/day, preferably 5 to 25 mg/kg/day, in single or 2 to 4 divided doses, as indicated by the carageenan oedema assay in rats. The active substance may be utilized in compositions such as tablets, capsules, solutions or suspensions containing up to about 300 mg. per unit of dosage of a compound or mixture of compounds of formula I or physiologically acceptable acid addition salt thereof. They may be compounded in conventional manner with a physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer or flavor, as called for by accepted pharmaceutical practice. Topical preparations containing about 0.01 to 3 percent by weight of active substance in a lotion, salve or cream may also be used.

The following examples are illustrative of the invention. All temperatures are on the centigrade scale.

Example 1.

4 - Butylamino - 1 - ethyl - 1H - pyrazolo-[3,4 - b]pyridine - 6 - carboxylic acid

a) 1 - ethyl - 4 - hydroxy - 1H - pyrazolo-[3,4 - b]pyridino - 6 - carboxylic acid ethyl ester

111 g. of 5 - Amino - 1 - ethylpyrazole (1 mol.) and 210 g. of sodium oxalacetic acid ethyl ester (1 mol.) are refluxed in 1 liter of acetic acid for 5 hours. After this period the acetic acid is removed in vacuo and the residue is treated with water. 1 - Ethyl - 4 - hydroxy-1H - pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester solidifies, is filtered off and recrystallized from methanol, m.p. 178—180°, yield 198 g. (84%).

b) 4 - ethoxy - 1 - ethyl - 1H - pyrazolo-[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester

23.5 g. of 1 - Ethyl - 4 - hydroxy - 1H-pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester (0.1 mol.) are dissolved in 100 ml. of anhydrous dimethylformamide. 22 g. of potassium carbonate (0.15 mol.) and 19 g. of ethyl iodide (0.12 mol.) are added and the mixture is heated with stirring for 10 hours at 50°. The precipitate is filtered off and the filtrate is treated with water. 4 - Ethoxy-1 - ethyl - 1H - pyrazolo[3,4 - b]pyridine-6 - carboxylic acid ethyl ester solidifies on cooling and is recrystallized from ligroin, m.p. 36—38°, yield 19.5 g. (74%).

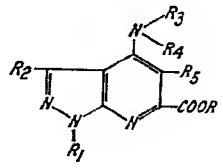
c) 4 - Butylamino - 1 - ethyl - 1H-pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester

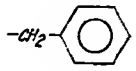
26.3 g of 4 - Ethoxy - 1 - ethyl - pyrazolo-[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester (0.1 mol.) are refluxed for 10 hours in 50 ml. of n-butylamine. After evaporation of the excess butylamine in vacuo, the residual crystalline 4 - butylamino - 1 -ethyl - pyrazolo-[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester is recrystallized from ligroin, m.p. 69—70°, yield 21 g. (72%).

d) 4 - butylamino - 1 - ethyl - 1H-pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid

14.5 g of 4 - Butylamino - 1 - ethyl-pyrazolo[3,4 - b] - pyridine - 6 - carboxylic acid ethyl ester (0.05 mol.) are heated for 10 hours at 80° in an ethanolic solution of 4.2 g. of potassium hydroxide (0.075 mol.). After this period, the mixture is evaporated to dryness, the residue is dissolved in 50 ml. of water and acidified with acetic acid. 4-Butylamino - 1 - ethyl - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid solidifies, is filtered off and recrystallized from acetic acid, m.p. 195—197°, yield 10.5 g. (80%).

According to the foregoing procedure, the following compounds are prepared:



Example	R_1	R_2	R_3	R_4	R_5	R
2	$-C_2H_5$	CH_3	H	C_4H_9	H	C_2H_5
3	$-C_2H_5$	H	CH_3	CH_3	H	C_2H_5
4	$-C_2H_5$	H	H		H	C_2H_5
5	$-C_2H_5$	H	H		H	H
6		CH_3	$-CH_2-CH_2-CH_2-CH_2-CH_2-$		H	C_2H_5
7	$-C_2H_5$	H	H	sec. C_4H_9	CH_3	C_2H_5
8	$-C_2H_5$	H	H	sec. C_4H_9	CH_3	H

Example 9.

4 sec.Butylamino - 1H - pyrazolo[3,4 - b]-pyridine - 6 - carboxylic acid ethyl ester

a) 1 - Furfuryl - 4 - hydroxy - 1H-pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester

163 g. of 5 - amino - 1 - furfurylpyrazole (1 mol.) and 210 g. of sodium oxalacetic acid ethyl ester (1 mol.) are refluxed in 1 liter of acetic acid for 3 hours. The solvent is distilled off and the residue is treated with water. 1 - Furfuryl - 4 - hydroxy - 1H-pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester crystallizes and is filtered off then recrystalilzed from methanol, m.p. 220—221°, yield 190 g. (73%).

b) Ethoxy - 1 - furfuryl - 1H - pyrazolo-[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester

28.7 g. of 1 - furfuryl - 4 - hydroxy - 1H-pyrazolo[3,4 - b]pyridine ethyl ester (0.1 mol.) are dissolved in 100 ml. of dimethylformamide. 22 g. of potassium carbonate (0.15 mol.) and 19 g. of ethyl iodide (0.12 mol.) are added and the mixture is heated with stirring for 10 hours at 60°. The precipitate is filtered off, the filtrate is treated with water. 4 - Ethoxy - 1 - furfuryl - 1H - pyrazolo-[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester solidifies on cooling and is recrystallized from methanol, m.p. 45—47°, yield 21.5 g. (68%).

c) 4 - Ethoxy - 1H - pyrazolo[3,4 - b]-pyridine - 6 - carboxylic acid ethyl ester.

3.2 g. of 4 - Ethoxy - 1 - furfuryl - 1H-pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester (0.01 mol.) and 1.5 g. of selenium dioxide (0.013 mol.) are heated in 10 ml. of diethyleneglycol dimethylether for 1.5 hours at 160°. The solution is filtered hot and the filtrate is cooled in an ice bath. 4-Ethoxy - 1H - pyrazolo[3,4 - b]pyridine - 6-carboxylic acid ethyl ester crystallizes and is recrystalilzed from butyl alcohol, yield 1.5 g. (64%).

d) 4 - sec.Butylamino - 1H - pyrazolo-[3,4 - b]pyridine -6 - carboxylic acid ethyl ester

2.5 g. of 4 - Ethoxy - 1H - pyrazolo[3,4-b]pyridine - 6 - carboxylic acid ethyl ester (0.01 mol.) are refluxed for 24 hours with 10 ml. of sec. butylamine. After this time, water is added and the crystalline 4-sec. butylamino - 1H - pyrazolo[3,4 - b]pyridine - 6-carboxylic acid ethyl ester is filtered off then recrystallized from butanol, m.p. 158—160°, yield 2.2 g. (83%).

Example 10.

4 - Butylamino - 1 - ethyl - 5 - methylpyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester

a) 1 - Ethyl - 4 - hydroxy - 5 - methylpyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester

111 g. of 5 - Amino - ethylpyrazole (1 mol.) and 202 g. of oxalopropionic acid ethyl ester (1 mol.) are heated in 1 liter of acetic acid for 3 hours under reflux. The solvent is distilled off and the residue is recrystallized from ethanol, yield 185 g. of 1 - ethyl - 4-hydroxy - 5 - methylpyrazolo[3,4 - b]pyridine-6 carboxylic acid ethyl ester (68%), m.p. 201—203°.

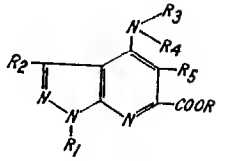
b) 4 - Ethoxy - 1 - ethyl - 5 - methylpyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester

24.9 g. of 1 - Ethyl - 4 - hydroxy - 5-methylpyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester (0.1 mol.), 22 g. of potassium carbonate (0.15 mol.) and 23 g. of ethyl iodide are heated in 150 ml. of dimethylformamide for 10 hours at 60° with continuous stirring. The excess potassium carbonate and potassium iodide are filtered off and water is added to the filtrate. 4 - Ethoxy-1 - ethyl - 5 - methylpyrazolo[3,4 - b]-pyridine - 6 - carboxylic acid ethyl ester solidifies and is recrystallized from methanol, yield 21.5 g. (78%), m.p. 54—56°.

c) 4 - Butylamino - 1 - ethyl - 5 - methylpyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester

2.8 g. of 4 - Ethoxy - 1 - ethyl - 5 - methylpyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester (0.01 mol.) and 10 ml. of n-butylamine are heated in an autoclave at 160° for 8 hours. After this time, the excess butylamine is evaporated and the residue is recrystallized from methanol, yield 2.2 g. (72%), m.p. 78—80°. TOhe hydrochloride salt is formed by adding to a solution containing 1 g. of this product in 10 ml. of ether, with cooling, 1 ml. of an alcoholic solution of hydrochloric acid.

The following additional products are made by the procedure of Example 1, 9 or 10:



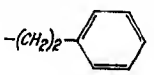
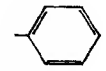
Example	R_1	R_2	R_3	R_4	R_5	R
11	CH_3-CH_2-	CH_3-	CH_3-CH_2-	CH_3-CH_2-	C_2H_5	C_2H_5-
12	CH_3-CH_2-	H	$-CH_2-CH_2-N(CH_3)-CH_2-CH_2-$		H	C_2H_5-
13	CH_3-CH_2-	H	$-(CH_2)_3N(C_2H_5)_2$	H	CH_3	C_2H_5
14	CH_3-CH_2-	H	$-CH_2-CH_2-CH_2-CH_2-CH_2-$		H	C_2H_5
15	CH_3-CH_2-	C_2H_5	CH_3-CH_2-	CH_3-CH_2-		C_2H_5
16	CH_3-CH_2-	H	$-(CH_2)_2N(C_2H_5)_2$	H	H	C_2H_5
17	CH_3-CH_2-	CH_3	H	H		C_2H_5
18	CH_3-CH_2-	H	$-C(CH_3)=CH-C(CH_3)=N-$		C_2H_5	C_2H_5
19	CH_3-CH_2-	CH_3	$-CH_2-CH_2-CH_2-CH_2-$		H	C_2H_5
20	CH_3-CH_2-	H	$-CH_2-CH_2-N(CH_2-CH_2-OH)-CH_2-CH_2-$		H	C_2H_5
21	CH_3-CH_2-	H	H	H		H
22	CH_3	H	$-(CH_2)_3CH_3$	H	H	C_2H_5

TABLE (Continued)

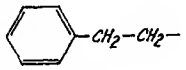
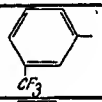
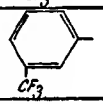
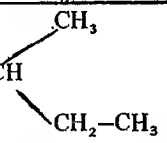
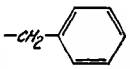
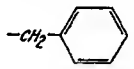
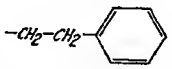
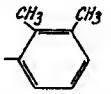
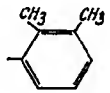
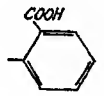
Example	R_1	R_2	R_3	R_4	R_5	R
23	CH_3	H	$-(CH_2)_3CH_3$	H	CH_3	H
24	CH_3-CH_2-	H	$-CH=C(CH_3)-C=C(CH_3)-NH-$		H	C_2H_5
25		H	$-(CH_2)_3CH_3$	H	H	C_2H_5
26	CH_3-CH_2-	H		H	H	C_2H_5
27	CH_3-CH_2-	H		H	CH_3	H
28	CH_3-CH_2-	H		H		C_2H_5
29	CH_3-CH_2-	H		H	CH_3	C_2H_5-
30	CH_3-CH_2-	H		H	H	C_2H_5-
31	CH_3-	H	$-CH(CH_3)_2$	H	H	C_2H_5-
32	CH_3-CH_2-	H	$-(CH_2)_5CH_3$	H	H	C_2H_5-
33		CH_3-	$-(CH_2)_3CH_3$	H	H	C_3H_7-

TABLE (Continued)

Example	R_1	R_2	R_3	R_4	R_5	R
34	$CH_3-(CH_2)_3-$	H		H	H	C_2H_5
35	CH_3-CH_2-	H		H	CH_3	C_2H_5
36	CH_3-CH_2-	H		H	H	H
37	CH_3-CH_2-	H		H	H	C_2H_5
38	$CH_3(CH_2)_3-$	CH_3-	$-(CH_2)_3CH_3$	H	CH_3	C_2H_5
39		H	$-(CH_2)_3CH_3$	H	CH_3	C_2H_5

Example 40.

4 - Butylamino - 5 - chloro - 1 - ethyl - 1H-pyrazolo[3,4 - b]pyridine - 5 - carboxylic acid ethyl ester

1) 5 - Chloro - 1 - ethyl - 4 - hydroxy-1H - pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester

111 g of 5 - Amino - 1 - ethyl - pyrazole (1 Mol) and 222 g of chloro-oxalo acetic acid, ethyl ester are refluxed in 1 ltr. of acetic acid for 4 hours. The acetic acid is removed in vacuo, and the solid residue is recrystallized from methanol. Yield 211 g (78%), m.p. 183—184°.

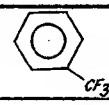
2) 5 - Chloro - 4 - ethoxy - 1 - ethyl-1H - pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid, ethyl ester

26.9 g of 5 - Chloro - 1 -ethyl - 4 - hydroxy-1H - pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid, ethyl ester (0.1 Mol) are dissolved in 100 ml of DMF. 21 g of Potassium-carbonate (0.15 Mol) and 18.6 g of ethyl iodide (0.12 Mol) are added and the mixture is kept at 60° with stirring for 10 hours. The undissolved material is filtered off and water is added. The 5 - chloro - 4 - ethoxy-1 - ethyl - 1H - pyrazolo[3,4 - b]pyridine-6 - carboxylic acid ethyl ester solidifies and is recrystallized from petrol ether. Yield 20.5 g (69%), m.p. 36—37°.

3) 4 - Butylamino - 5 - chloro - 1 - ethyl-1H - pyrazolo[3,4 - b]pyridine - 6 - carboxylic acid ethyl ester

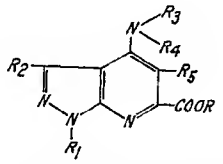
2.9 g of 5 - Chloro - 4 - ethoxy - 1-ethyl - 1H - pyrazolo[3,4 - b]pyridine - 6-carboxylic acid, ethyl ester (0.01 Mol) are refluxed in 10 ml of n-butylamine for 48 hours. The excess amine is distilled off and the residue is recrystallized from petrol ether. Yield 2.5 g (78%), m.p. 71—73°.

According to the foregoing procedure the following compounds have been prepared:

Example	R_1	R_2	R_3	R_4	R_5	R
41	C_2H_5	H	H	H	Cl	C_2H_5
42	C_2H_5	CH_3	C_4H_9	H	Cl	C_2H_5
43	$-CH(CH_3)_2$	H	C_3H_7	H	Br	C_2H_5
44	C_2H_5	H		H	Cl	C_2H_5
45	C_2H_5	H	$-CH_2-CH_2-CH_2-CH_2-CH_2-$		Cl	C_2H_5
46	C_2H_5	CH_3		H	Br	C_2H_5
47	C_2H_5	H	C_2H_5	C_2H_5	Cl	C_2H_5

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein R is hydrogen or lower alkyl; R_1 is hydrogen, lower alkyl, phenyl or phenyl-lower alkyl; R_2 is hydrogen or lower alkyl; R_3 and R_4 each is hydrogen, lower alkyl, phenyl, R_6, R_7-phenyl, R_8, R_7-phenyl-lower alkyl or di-lower alkylamino-lower alkyl, or R_3 and R_4 together with the nitrogen to which they are attached form one of the heterocyclics R_8, R_9-pyrrolidino, R_8, R_9-piperidino, R_8, R_9-pyrazolyl, R_8, R_9-dihydropyridazinyl or R_8, R_9-piperazinyl; R_5 is hydrogen, lower alkyl, phenyl, phenyl-lower alkyl or halogen; R_6 and R_7 each is hydrogen, lower alkyl, trifluoromethyl or carboxy; R_8 and R_9 each is hydrogen, lower alkyl or hydroxy-lower alkyl, or such a compound in the form of a physiologically acceptable acid addition salt.

2. A compound as in Claim 1 wherein R is hydrogen or lower alkyl, R_1 is hydrogen, ethyl or butyl, R_2 is hydrogen or methyl, R_3 is ethyl, propyl or butyl, R_4 is hydrogen or ethyl and R_5 is hydrogen or methyl.

3. A compound as in Claim 1 wherein R, R_1 and R_3 each is lower alkyl, and R_2, R_4 and R_5 each is hydrogen.

4. A compound as in Claim 3 wherein R and R_1 each is ethyl and R_3 is butyl.

5. A compound as in Claim 1 wherein R_1 and R_3 each is lower alkyl and R, R_2, R_4 and R_5 each is hydrogen.

6. A compound as in Claim 5 wherein R_1 is ethyl and R_3 is butyl.

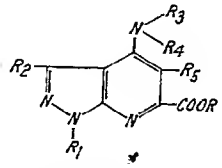
7. A compound as in Claim 1 wherein R and R_3 each is lower alkyl and R_1, R_2, R_4 and R_5 each is hydrogen.

8. A compound as in Claim 7 wherein R is ethyl and R_3 is butyl.

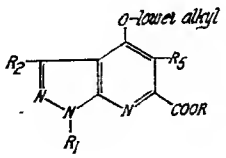
9. A compound as in Claim 1 wherein R, R_1, R_3 and R_5 each is lower alkyl and R_2 and R_4 each is hydrogen.

10. A compound as in Claim 9 wherein R and R_1 each is ethyl, R_3 is butyl and R_5 is methyl.

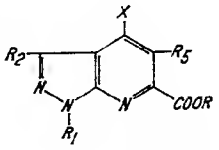
11. A process for the production of a compound of the formula



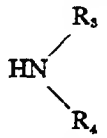
wherein R is hydrogen or lower alkyl; R_1 is hydrogen, lower alkyl, phenyl or phenyl-lower alkyl; R_2 is hydrogen or lower alkyl; R_3 and R_4 each is hydrogen, lower alkyl, phenyl, R_6, R_7-phenyl, R_6, R_7-phenyl-lower alkyl or di-lower alkylamino-lower alkyl, or R_3 and R_4 together with the nitrogen to which they are attached from one of the heterocyclics R_8, R_9 - pyrrolidino, R_8, R_9 - piperidino, R_8, R_9 - pyrazolyl, R_8, R_9 - dihydropyridazinyl or R_8, R_9-piperazinyl; R_5 is hydrogen, lower alkyl, phenyl, phenyl-lower alkyl or halogen; R_6 and R_7 each is hydrogen, lower alkyl, trifluoromethyl or carboxy, R_8 and R_9 each is hydrogen, lower alkyl or hydroxy-lower alkyl, or such a compound in the form of a physiologically acceptable acid addition salt, which comprises reacting a compound of the formula



or



wherein R, R_1, R_2 and R_5 have the same meaning as defined above and X is chlorine or bromine, with an amine of the formula



wherein R_3 and R_4 have the same meaning as defined above.

12. A compound according to claim 1 as named in any of the Examples.

13. A process according to claim 11 substantially as hereinbefore described in any of the Examples.

14. A compound according to claim 1 when prepared by a process according to claim 11 or 13.

15. A pharmaceutical preparation comprising a compound according to any one of claims 1 to 10, 12 or 14 and a pharmaceutical carrier.

16. A pharmaceutical preparation according to claim 15 wherein the carrier is solid.

17. A pharmaceutical preparation according to claim 15 wherein the carrier is liquid and contains a preservative, stabilizer or flavour.

18. A pharmaceutical preparation according to claim 15 in the form of a tablet, capsule or sterile injectable preparation.

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